



**NTP**  
National Toxicology Program

# Research Concept: Nanoscale gold

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NTP Board of Scientific Counselors Meeting

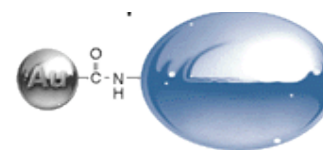
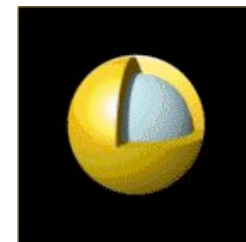
December 6th, 2007





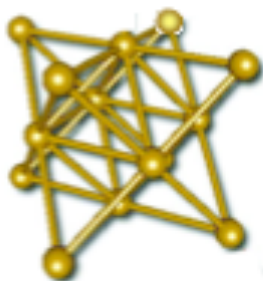
## Uses of nanoscale gold

- Biomedical
  - Targeted chemotherapy/photodynamic therapy.
  - Topical applications for acne/psoriasis
  - Dental and bone implants
  - Colloidal gold-Alternative medicine
  - Antimicrobial coatings
  - In vivo imaging, contrast agents
  - Ex vivo diagnostic devices
- Electronics
  - Use as nanorods and nanowires for commercial applications
- Catalysts
  - Supported (gas and liquid phase) and soluble
- Cosmetics

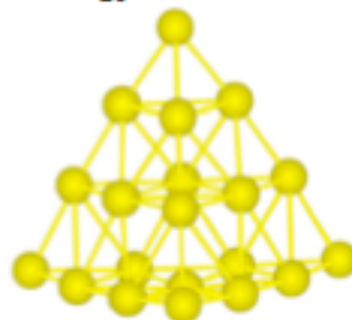




**Au<sub>14</sub>**



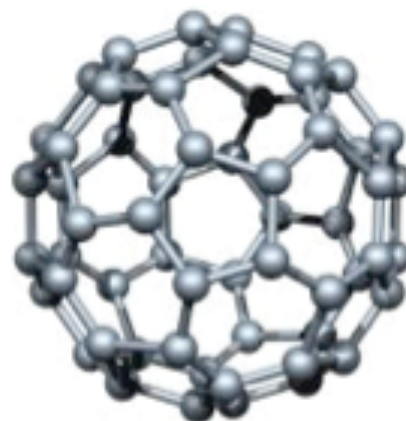
**Au<sub>20</sub>**



**Au<sub>55</sub>**



**Fullerene C<sub>60</sub>**



1 nm

## Relative sizes

18nm x 300nm  
Tobacco mosaic virus



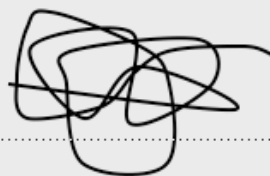
5nm  
hemoglobin



5nm wide:  
Lipid bilayer



2nm x 400nm  
Carbon nanotubes



1nm  
C60

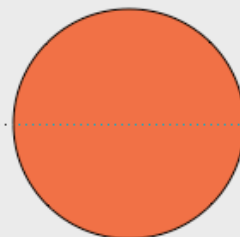
5nm  
G5 dendrimer



60nm  
Gold nanoshell



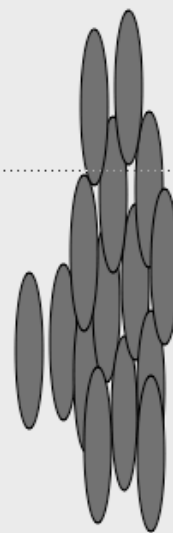
60nm  
Nano-C60



120nm  
HIV



40nm  
PEG-Qdot



14 nm x 81nm  
Rutile nano  $\text{TiO}_2$

1μm



## Some background on effects of gold/nanogold

- Gold
  - Gold is the most biologically inert metal
  - Occupational gold dermatitis, allergic reactions to Goldschlager
    - Due to dissolution of Au(0) to Au (I) or Au (II)?
- Nanoscale gold
  - Lack of toxicity of 1.9nm gold in after single dose
    - 3200 mg/kg for tumor bearing Balb/C, examined 1 year later.
    - Up to 700 mg/kg for CD-1 mice, examined 30 days later.
  - Some ADME studies
    - Oral: Uptake of 4, 10 nm and 28 but not 58nm Au nanoparticles from the gut
    - i.v.- Size and surface functional group can impact on the tissue distribution and whole body retention of the nanoscale gold
    - Inhalation: retention of 75% of 5-8nm Au particles after 6 hour inhalation study
  - No adequate in vivo toxicity studies using well characterized nanoscale gold of defined sizes and/or coating in the public literature.



## **Nominator (FDA-CSWG) recommendations**

- Conduct rodent based studies
  - Absorption, distribution, metabolism and elimination studies
    - Oral and intravenous routes of administration (including blood-brain transfer)
  - Single and repeat dose toxicity studies (28 days) in rodents
  - Subchronic, dose-response toxicity studies in rodents (only if warranted).
- The studies should be conducted on
  - Nanoscale gold of one or two sizes (e.g. 10 nm - 60 nm)
  - With and without surface coatings (e.g. polyethylene glycol or protein coated).
  - The nanoscale material should be thoroughly characterized before use, and after recovery from tissues.



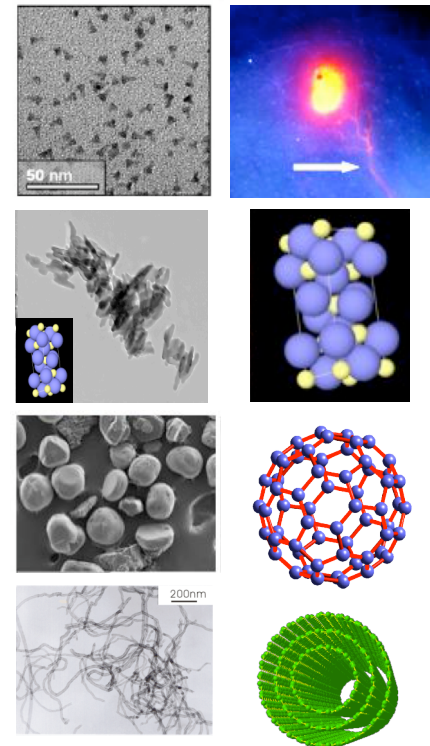
## Rationale for NTP studying nanoscale gold

- Significance and Public Health Impact
  - Primary focus is to increase our science base on the understanding how physiochemical properties impact on the ADME and toxicity of nanogold.
  - Widespread uncertainty in how to assess health risk of nanomaterials
  - Identified research need by FDA
    - May be used in their interpretation of the potential adverse biological and toxicological effects associated with exposure to nanoscale gold or products containing nanoscale gold
  - Anticipated that potential for exposure will increase as use increases
    - Actual exposure has not been quantified
- Project integrates with the NTP Nanotechnology Safety Initiative
  - Need to understand the effects of nanoscale materials in general before widespread exposure and/or effects have occurred
  - Identify key physicochemical properties that govern nanomaterial safety
  - Examine how nanomaterials enter, travel through, and deposit in the body
  - <http://ntp.niehs.nih.gov/go/nanotech>



## NTP Nanotechnology Safety Initiative

- Ongoing program of multiple classes of nanomaterials
- Studies ongoing/in development
  - Core shell structure
    - Quantum dots
  - Carbon fullerenes
  - Carbon nanotubes
  - Metal Oxides
    - Titanium dioxide
    - Ceric oxide
  - Dendrimers
  - Nanoscale metals
    - Nanoscale silver (reviewed at June 2007 BSC)
    - Nanoscale gold



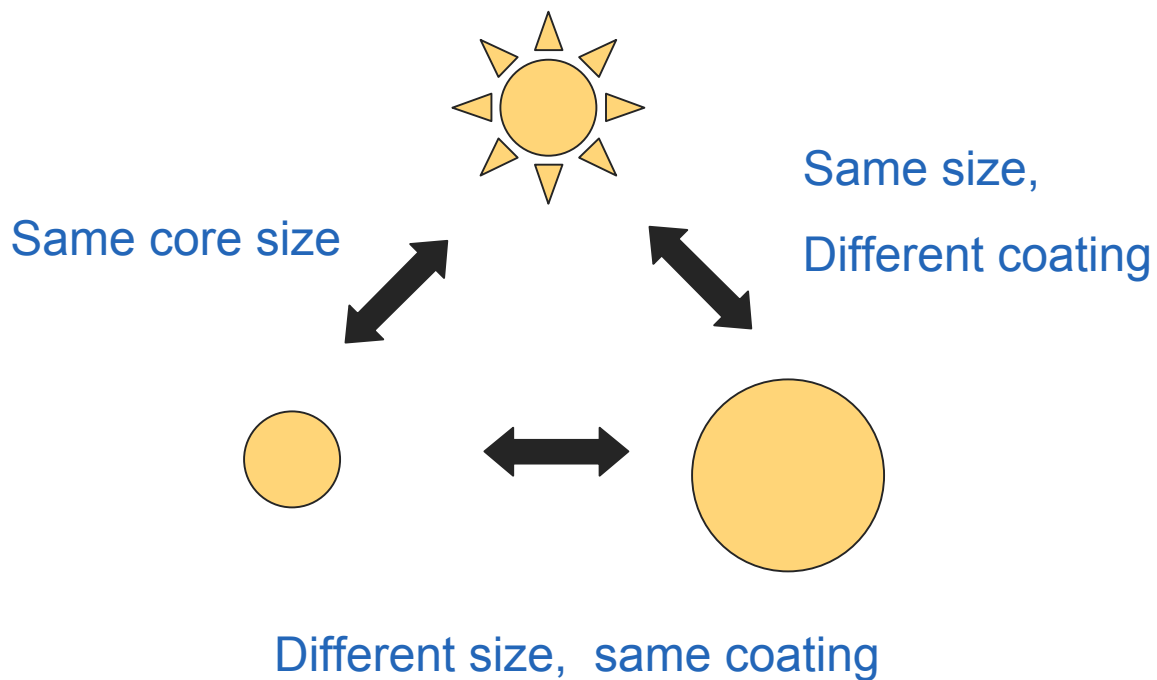


## Key issues/questions for nanogold

- Need for publicly available information regarding the ADME and in vivo toxicity of nanoscale materials
  - Especially the zero state metals (Au, Ag).
- How do surface modifications affect ADME?
  - Complete ADME profiles of thoroughly characterized nanoscale golds are not available.
  - ADME of Au-support particle vs the Au-surface modified particle
- Choice of surface coatings and sizes
  - # possible permutations of size, shape and the variety of coatings that are or could be applied to nanoscale gold in a commercial setting.
- Dose-metrics
  - Particle number-based and surface area-based metrics increase with decreasing particle size.
  - Mass-based potency may differ, but surface area-based potency may not



## Conceptual comparisons



- Two sizes of “uncoated” citrate-stabilized gold particles (from 10 nm to 100 nm).
- One “coated” nanoscale gold particle, surface functionalized with polyethylene glycol.



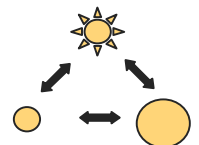
## Hypotheses to evaluate:

- That the pharmacokinetics and tissue distribution of nanoscale gold particles of different sizes, are the same.
- That the pharmacokinetics and tissue distribution of nanoscale gold particles of comparable size but with different surface modifications are the same.
- That the toxicity of nanoscale gold particles of different sizes are the same.
- That the toxicity of nanoscale gold particles of comparable size but with different surface modifications are the same.



## Aim 1

- Evaluate the effect of particle size and particle coatings on the pharmacokinetic profile of nanoscale gold.
  - Compare 3 specific nanogold preparations and conduct time course and tissue disposition studies in rodents (rats and mice).
  - Evaluate two sizes of “uncoated” citrate-stabilized particles (from 10 nm to 100 nm).
  - Evaluate one “coated” nanoscale gold particle (surface functionalized with polyethylene glycol).
- Evaluate tissue disposition after oral and intravenous administration.
  - Quantitation in tissues using established methods for analyses and, if feasible, location within tissues.
- Which nanogold particles to study?
  - Will be determined through discussion with scientists from NIST, FDA and NCIs Nanotechnology Characterization Laboratory.
  - NIST is developing 10, 30 and 60 nm gold standard reference materials





## Aim 2

- Evaluate the effect of particle size and particle coatings on the toxicological profile of nanoscale gold in vivo.
- We propose to compare the three nanogold preparations and evaluate and compare the toxicological profiles
  - Sub-acute and sub-chronic oral exposure in rodents.
  - Studies should consider an evaluation of potential systemic toxicity and organ specific toxicity and the potential for toxicity to the immune and nervous systems.

